PATENT COOPERATION TREATY

From the INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

10/537PCT

To:

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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	11.11.2004
Applicant's or agent's file reference: RLL-270WO	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IB 02/05220	10.12.2002	10.12.2002

Applicant: RANBAXY LABORATORIES LIMITED et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:

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Tel. +49 89 2399 - 0 Tx: 523656 epmu d
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Authorized Officer

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ENTERED

ATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference RLL-270WO	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/IB 02/05220	International filing date *(day/month/year)* 10.12.2002	Priority date *(day/month/year)* 10.12.2002
International Patent Classification (IPC) or both national classification and IPC C07D209/52		
Applicant RANBAXY LABORATORIES LIMITED et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
07.07.2004	11.11.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Kollmannsberger, M Telephone No. +49 89 2399-7364

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/IB 02/05220

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

2, 4-86	as originally filed
1, 3	filed with the demand

Claims, Numbers

1-38	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 9-22; 1-38 (insofar they relate to "prodrugs and metabolites")

   because:

   ☒ the said international application, or the said claims Nos. 9-22 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 1-38 (insofar they relate to "prodrugs and metabolites")

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/ or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-38 (insofar they do not relate to "prodrugs and metabolites")
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-38 (insofar they do not relate to "prodrugs and metabolites")
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-8, 23-38
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item III

III-1. Claims 9-22 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

III-2. The search report only covers compounds structurally defined in the claims (see ISR). "Prodrugs" and "metabolites" have not been searched. The preliminary examination is thus also limited to this subject-matter (Rule 66.1(e) PCT))

Re Item V

V-1. Prior Art

The following documents are considered relevant:

D1: EP-A-0930298
D2: WO-A-9745414
D3: EP-A-0823423
D4: EP-A-0863141
D5: US-A-5703091
D6: US-A-5914338
D7: US-A-5397800

V-2. Novelty (Art 33(2) PCT)

The compounds disclosed in D1-D4 differ from the claimed ones in that they have a piperidine instead of the claimed bicyclic systems. D5 discloses compounds showing i. a. the claimed azabicyclo-[3.1.0]-hexanes (see column 2) but the rest of the molecule is different. Also D7/D8 disclose bicyclic systems, but not the claimed ones and additionally the rest of the molecules are structurally different.

Art. 33(2) PCT is thus fulfilled for the present claims.

V-3. Inventive step (Art. 33(3) PCT)

D1-D7 all deal with compounds presenting antagonistic activity for muscarinic receptors. The problem to be solved by the present application is thus the provision of further compounds presenting this activity. Closest prior art can be seen in D1-D4 since these documents disclose compounds only differing in the nature of the heterocyclic system (piperidines instead of bridged piperidines). The above problem has been solved in a non-obvious manner. Although D5 discloses one of the claimed bicyclic systems in compounds presenting muscarinic receptor antagonistic activity, the present compounds are not considered to be obviously derivable from a combination of D1-D4 and D5 due to the structural didfferences of the compounds (the bicyclic ring is not N-substituted, the carbon attaced to two ring systems is missing etc).

Art. 33(3) PCT is thus fulfilled for the present claims.

3,6-DISUBSTITUTED AZABICYCLO [3.1.0] HEXANE DERIVATIVES AS MUSCARINIC RECEPTOR ANTAGONISTS

FIELD OF THE INVENTION

This invention relates to the derivatives of 3,6-disubstituted azabicyclo[3.1.0] hexanes. The compounds of this invention can function as muscarinic receptor antagonists, and can be used for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems mediated through muscarinic receptors.

The invention also relates to pharmaceutical compositions containing the compounds of the present invention and the methods of treating the diseases mediated through muscarinic receptors.

BACKGROUND OF THE INVENTION

Muscarinic receptors as members of the G Protein Coupled Receptors (GPCRs) are composed of a family of 5 receptor sub-types (M_1, M_2, M_3, M_4 and M_5) and are activated by the neurotransmitter acetylcholine. These receptors are widely distributed on multiple organs and tissues and are critical to the maintenance of central and peripheral cholinergic neurotransmission. The regional distribution of these receptor sub-types in the brain and other organs has been documented. For example, the M_1 subtype is located primarily in neuronal tissues such as cereberal cortex and autonomic ganglia, the M_2 subtype is present mainly in the heart where it mediates cholinergically induced bradycardia, and the M_3 subtype is located predominantly on smooth muscle and salivary glands (Nature, 1986; 323: 411; Science, 1987; 237: 527).

A review in Current Opinions in Chemical Biology, 1999; 3: 426, as well as in Trends in Pharmacological Sciences, 2001; 22: 409 by Eglen et. al., describe the biological potentials of modulating muscarinic receptor subtypes by ligands in different disease conditions like Alzheimer's disease, pain, urinary disease condition, chronic obstructive pulmonary disease etc.

A review in J. Med. Chem., 2000; 43: 4333 by Christian C. Felder et. al. describes therapeutic opportunities for muscarinic receptors in the central nervous

Pediatric Urology," ed. JY Gillenwatter, JT Grayhack, SS Howards, JW Duckett, pp 1220-1325, St. Louis, MO; Mosby. 3rd edition.)

Despite these advances, there remains a need for development of new highly selective muscarinic antagonists which can interact with distinct subtypes, thus avoiding the occurrence of adverse effects.

Compounds having antagonistic activity against muscarinic receptors have been described in Japanese patent application Laid Open Number 92921/1994 and 135958/1994; WO 93/16048; U.S. Patent No. 3,176,019; GB 940,540; EP 0325 571; WO 98/29402; EP 0801067; EP 0388054; WO 9109013; U.S. Patent No. 5,281,601. U.S. Patent Nos. 6,174,900, 6,130,232 and 5,948,792; WO 97/45414 are related to 1,4-disubstituted piperidine derivatives; WO 98/05641 describes fluorinated, 1,4-disubstitued piperidine derivatives; WO 93/16018 and WO96/33973 are other references.

A report in J. Med. Chem., 2002; 44:984, describes cyclohexylmethyl piperidinyl triphenylpropioamide derivatives as selective M_3 antagonist discriminating against the other receptor subtypes.

SUMMARY OF THE INVENTION

The present invention provides derivatives of 3,6-disubstituted azabicyclo[3.1.0]hexanes as muscarinic receptor antagonists and are useful for the safe and effective therapeutic or prophylactic agents for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems, and process for the synthesis of the novel compounds.

The invention also provides pharmaceutical compositions containing the compounds, and which may also contain acceptable carriers, excipients or diluents which are useful for the treatment of various diseases of the respiratory, urinary and gastrointestinal systems.

The present invention also includes within its scope prodrugs of the compounds. In general, such prodrugs are functionalized derivatives of these compounds which readily get converted *in vivo* into the defined compounds.